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Journal

The Journal of cell biology, 154(2)

ISSN

0021-9525

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Publication Date

2001-07-01

DOI

10.1083/jcb.200101097

Peer reviewed

Mitosis, microtubules, and the matrix

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The mechanical events of mitosis depend on the action of microtubules and mitotic motors, but whether these spindle components act alone or in concert with a spindle matrix is an important question.

Understanding the mechanism of mitosis is a problem that has fascinated and frustrated cell biologists for over a century (Mitchison and Salmon, 2001). Fifty years ago, Ostergren (1950) commented, "The biological system of the spindle and the chromosomes is obviously a very complicated one. It can by no means be taken for granted that the mechanical factors working in this system are of a simple and easily analyzable form." This statement remains true, despite the great progress that has been made in the molecular identification of many factors that are important for spindle mechanics. For example, there is widespread agreement that the dynamic properties of microtubules (MTs)* and the interactions between spindle MTs and MT-based motor proteins play critical roles in spindle formation and function, although there is healthy debate concerning the precise roles played by each of these factors (Inoue and Salmon, 1995; Compton, 2000; Sharp et al., 2000a; Wittman et al., 2001). Mitotic motors act by diverse mechanisms, with some motors influencing MT dynamics, whereas others drive the sliding of MTs relative to chromosomes, to centrosomes, to the cell cortex, or to adjacent MTs (Sharp et al., 2000a). However, while the aforementioned spindle components are clearly important, there remains a lurking suspicion among students of mitosis that something is missing, that spindles contain another, ill-defined mechanical component referred to as "the spindle matrix," which could help organize and stabilize spindle MTs and serve as a stationary substrate against which motors slide MTs. Obtaining definitive evidence for the existence and identity of this spindle matrix has proved to be one of the least "easily analyzable" problems in mitosis research, but an interesting paper by Walker et al. (2000) introduces a new candidate for study in this context, *Drosophila* skeletor.

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*Abbreviations used in this paper: ip, interpolar; MT, microtubule.

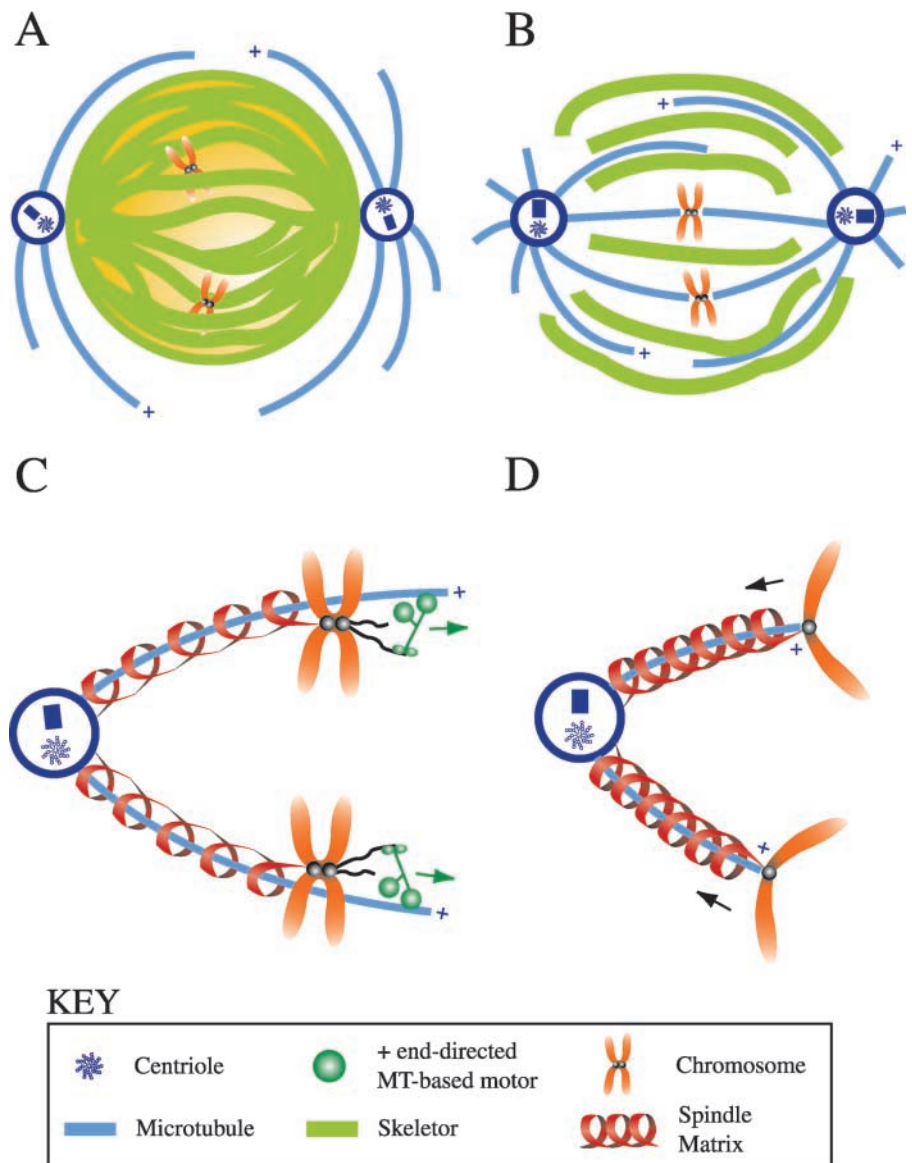
Skeletor as a matrix molecule

Skeletor was discovered through the use of an mAb which, by immunofluorescence, displayed an intriguing dynamic nuclear staining pattern in *Drosophila* embryos and was used in expression cloning to identify the skeletor ORF (Walker et al., 2000). The skeletor gene lies within a complex locus that encodes two mRNAs, the first of which encodes a 32-kD cytoplasmic polypeptide unrelated to skeletor, whereas the second is proposed to encode two polypeptides, an 85-kD polypeptide that cannot be detected in embryonic extracts and an 81-kD, 744-residue nuclear protein that is recognized by several antibodies raised against a GST fusion protein containing part of this sequence. The latter, 81-kD polypeptide is skeletor, and its distribution and function were probed using one of the antibodies that detect it, an IgM named mAb1A1.

By immunofluorescence staining with mAb1A1, skeletor displays a similar distribution to chromatin in interphase embryonic nuclei and localizes to polytene chromosomes in larval squashes. During prophase, however, skeletor appears to dissociate from chromatin, associating with the nuclear envelope and also forming an intranuclear spindle-shaped structure that precedes the assembly of the MT-based spindle (Fig. 1). Skeletor and MTs display a similar distribution through anaphase, but by telophase skeletor appears to reassociate with chromatin within daughter nuclei. The microinjection of mAb1A1 leads to the formation of embryos containing mislocalized and fragmented nuclei, consistent with a role for skeletor in nuclear organization and division.

What type of mechanical function might skeletor perform in spindles? It is apparent from Fig. 3, G–H of Walker et al. (2000), that skeletor displays a particularly striking association with the interpolar (ip) MT bundles that cross the spindle midzone in embryonic metaphase spindles. These ipMT bundles contain abundant parallel MTs near the poles, but the density of MTs decreases in the region of antiparallel overlap at the midzone and the bipolar kinesin, KLP61F, is found along the length of these bundles (Sharp et al., 1999). Therefore, it is appealing to speculate that skeletor could serve as a matrix that stabilizes these bundles, particularly at the midzone, and it could act as a substrate that anchors motors like KLP61F, allowing them to slide MTs relative to the matrix as well as to each other (Walczak and Mitchison, 1996).

The observation that the "skeletor spindle" forms before the assembly of the MT-based spindle and subsequently persists following MT depolymerization is consistent with the



idea that it is an MT-independent structure that could guide the formation and function of the MT spindle (Fig. 1, A and B). However, the colocalization between skeleton and MTs is not exact; little skeleton is seen associated with the interzonal and midbody MTs responsible for anaphase B and telophase nuclear positioning, so an alternative interpretation is that the spindle shape of the skeleton-bound structures could reflect the sequestration of skeleton within the nuclear/spindle envelope that remains largely intact throughout mitosis in *Drosophila* embryos (Stafstrom and Staehelin, 1984).

In vitro binding, MT assembly, and motility assays using purified skeleton and MT proteins might be useful for testing the idea that skeleton stabilizes MT bundles and acts as a substrate for anchoring MT motors. In addition, the analysis of mutant flies containing functionally impaired skeleton protein might be useful in further localizing and testing the function of skeleton in spindles. The results obtained by Walker et al. (2000) on the localization and function of skeleton are intriguing, but the fact that mAb1A1 does not rec-

ognize the skeleton polypeptide on immunoblots, and that precleared ascitic fluid rather than purified IgM's were used in the microinjection experiments, raise concerns about possible technical artifacts.

Thus, skeleton appears to be a component of something very interesting, but what? Is it a bona fide spindle matrix that acts as a mechanical scaffold for MT and motor function, a nuclear matrix with MT-independent functions, or something else, for example a membranous reticulum that controls spindle function by regulating the concentration of ions within the nucleus? In this respect, skeleton joins a long list of intriguing spindle structures, including the electron-dense "collar" of diatom spindles (Pickett-Heaps et al., 1982), the "spoke" protein, NuMA protein and midbody matrix of mammalian cells (Sellitto and Kuriyama, 1988; Paddy and Chelsky, 1991; Dionne et al., 1999), and the kinesin-binding remnant of sea urchin embryonic spindles (Leslie et al., 1987), all of which have been described as candidates for functioning as spindle matrices.

The microtrabecular lattice as a spindle matrix

Pickett-Heaps et al. (1982) proposed the provocative idea that spindles contain a "microtrabecular lattice" that acts as a spindle matrix which could participate in prometaphase and anaphase chromosome movements. In this model, it was proposed that the diatom spindle collar represents an elastic spindle matrix corresponding to the microtrabecular lattice, which tends to collapse around each spindle pole within each half spindle, but could be stretched out in an antipolar direction along MTs in an endergonic process. The antipolar stretching of the matrix was proposed to be driven by a plus end-directed MT motor (Fig. 1 C). Chromosomes would attach to the periphery of the matrix and consequently the concerted action of the MT motor stretching the matrix with attached chromosomes in a plateward direction, together with the antagonistic poleward-directed elastic recoil of the matrix, would give rise to the bidirectional movements of chromosomes observed throughout mitosis (Fig. 1 D).

Apparent support for this model emerged from the observation that kinesin and a kinesin-like protein appeared to associate with spindle-shaped remnants, perhaps corresponding to spindle matrices, that were left behind following the extraction of MTs from sea urchin and diatom spindles, respectively (Scholey et al., 1985; Pickett-Heaps, 1986; Leslie et al., 1987; Wein et al., 1998). The nature of the remnant in diatom spindles is unknown, but subsequent work revealed that the sea urchin kinesin-associated spindle remnant consists of elements derived from spindle-associated membranes that normally form vesicles which are moved out along astral MTs to the cell surface for Ca^{++} -regulated exocytosis (Wright et al., 1991, 1993; Bi et al., 1997). Furthermore, the Pickett-Heaps et al. (1982) model was based largely on the perceived similarity between chromosome movements in living cells and pigment granule movements in melanophores; both types of bidirectional motility were proposed to depend on the action of a plus end-directed MT motor that worked antagonistically to an elastic net that tended to collapse the chromosomes or pigment granules polewards. It is now clear that the bidirectional movements of pigment granules can be explained by the action of antagonistic plus and minus end-directed MT-based motor proteins, and there is no need to invoke the action of any type of contractile matrix to explain granule behavior (Rogers et al., 1997). Thus, the similar appearance of bidirectional movements of chromosomes and pigment granules might depend upon their common use of plus and minus end-directed MT motor activities. In summary, this body of work does not provide compelling evidence for the existence of a spindle matrix.

However, this does not prove that the microtrabecular spindle matrix does not exist. Based on the observation that the ability of kinetochore fibers to generate poleward forces on kinetochores appears to persist after they have been severed using a UV microbeam, Pickett-Heaps et al. (1997) propose that the contraction of an elastic matrix that links kinetochores to poles pulls chromatids polewards during anaphase, with the MTs acting as rigid struts that govern the rate of elastic recoil. In these experiments, the UV irradiation produces areas of reduced birefringence which are depleted of MT polymer, but the efficiency of MT depletion is

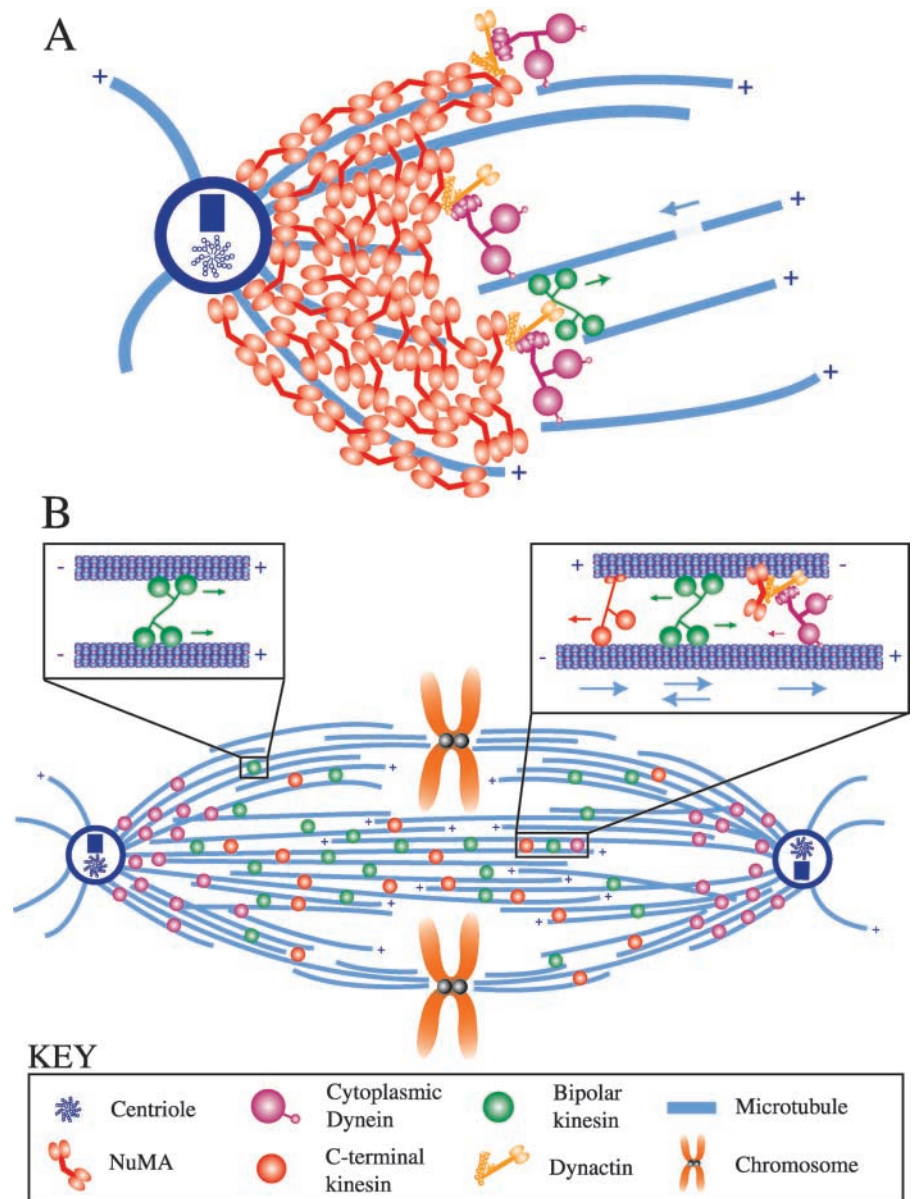
unknown. Moreover, it is unclear why the protein making up the proposed matrix would not itself be destroyed by the UV microbeam. We note that MTs appear to be cross-linked throughout the spindle, forming a continuum in which kinetochore fibers are connected to adjacent ipMT bundles (Mastronarde et al., 1993). It is possible that mechanical connections between the kinetochore stubs produced by UV irradiation and adjacent ipMTs could explain the observations described by Pickett-Heaps et al. (1997). Furthermore, based on the effects of severing spindles using glass microneedles instead of UV irradiation, Niklas (1989) argued that the motor for anaphase A is likely to be located at or near the kinetochore, rather than being distributed all along the kinetochore fiber. Therefore, at the present time no definitive evidence for the existence or molecular identity of the presumed microtrabecular matrix exists, although the localization of skeleton in anaphase spindles makes it a potential candidate.

NuMA and spindle pole organization

More recently, it has been proposed that a spindle matrix composed primarily of a highly branched and cross-linked lattice of the NuMA protein is required for the proper formation and function of spindle poles (Dionne et al., 1999). This hypothesis is based largely on three lines of study. The first is that NuMA has been shown to become highly enriched at the spindle poles in most vertebrate cell types (Lydersen and Pettijohn, 1980). Thus, it is appropriately positioned to carry out a function at the spindle poles. Secondly, the polar localization of NuMA is thought to require MT tracks only for its establishment, becoming insoluble to MT depolymerization thereafter (Dionne et al., 1999). Thirdly, NuMA is an elongated, highly α -helical protein (Yang et al., 1992) capable of multimerization (Saredi et al., 1996; Harborth et al., 1999), suggesting that it has the intrinsic capacity to form higher order assemblies within the cell. Therefore, it has been argued that, given the ability of NuMA to associate both with MTs and the dynactin complex, such a NuMA matrix could plausibly anchor and stabilize spindle MTs and provide a stationary substrate for the activity of a variety of mitotic motors, including the plus end-directed bipolar kinesin (which accumulates at the poles in frog extract spindles; Kapoor et al., 2000) and the minus end-directed cytoplasmic dynein (Blangy et al., 1997; Merdes and Cleveland, 1997; Dionne et al., 1999). In turn, these activities could focus the minus ends of MTs at the poles, attach centrosomes to the poles, and drive MT flux (Fig. 2 A).

Yet, although functional analyses have clearly established that NuMA plays an integral mitotic function (Compton, 2000), the evidence that it is a true matrix protein is circumstantial and there are some interesting alternative hypotheses which could explain many of the aforementioned observations without invoking a NuMA matrix (Merdes and Cleveland, 1997; Merdes et al., 2000; Wittman et al., 2001). For example, one alternative hypothesis posits that NuMA acts as a receptor or adaptor molecule for dynein/dynactin, allowing the motor to assemble into multivalent structures that are capable of forming cross-links between adjacent spindle MTs at the poles. Such an activity is appealing because it provides an underlying mechanism for dynein-mediated MT-MT sliding, an

Figure 2. The NuMA matrix and MT–MT cross-linking motors. (A) The NuMA matrix. The NuMA protein oligomerizes into a highly branched and cross-linked lattice around the spindle poles. Because NuMA is believed to associate with both microtubules and certain mitotic motors, such a matrix could anchor and cross-link microtubules and also immobilize motors at or near the poles. The latter activity would provide a stationary substrate for motor-driven MT transport within the spindle, allowing minus end-directed motors such as cytoplasmic dynein to focus the minus ends of MTs at the poles and plus end-directed motors such as bipolar kinesins to cross-link polar microtubules into asters and drive the poleward flux of kinetochore microtubules. (B) A matrix of MT–MT cross-linking and sliding motors. The spindle is packed with a dense array of MT–MT cross-linking and sliding motors. Specific interactions that occur between these motors and spindle MTs drive the formation and function of the spindle. (Inset, top left) Bipolar kinesins such as KLP61F can cross-link parallel MTs into bundles, thus contributing to the organization of MTs in the half spindles, but generate no net axial force between them. (Inset, top right) In contrast, when bipolar kinesins cross-link antiparallel MTs into bundles, they can generate paraxial force and thus slide them in relation to one another. Asymmetric motors like dynein and Ncd can presumably cross-link and slide either parallel or antiparallel MTs in relation to one another, dependent upon the nature of the binding between their nucleotide-insensitive MT binding site and the MT surface lattice, and the polarity of motion driven by their motor domains.



activity that has been observed in frog extract spindles (Heald et al., 1997). It is also plausible that multivalent NuMA complexes, transported to the spindle poles by dynein, could directly cross-link MTs into bundles and focus the poles.

Cell types that lack NuMA might utilize analogous proteins to focus spindle poles. For example, it has recently been proposed that the MT-associated protein, Asp, functionally substitutes for NuMA in spindles of *Drosophila*, whose genome apparently does not encode a NuMA homologue (Wakefield et al., 2001). Thus, the Asp protein is proposed to accumulate at the minus ends of spindle MTs localized at the poles or at the peripheral edges of the central spindle, where it cross-links MTs and thus focuses MTs at the poles and contributes to the bundling of MTs in the central spindle (Wakefield et al., 2001). Another candidate is a protein complex consisting of two MT-associated proteins, Msps and D-TACC, which are proposed to regulate MT stability and organization at spindle poles in *Drosophila* (Cullen and Ohkura, 2001; Lee et al., 2001). Immunofluorescence sug-

gests that these proteins assemble into a centrosome-like structure that stabilizes the poles of anastral mitotic spindles.

MTs and MT cross-linking/sliding motors as a spindle matrix

It is plausible that a novel spindle matrix is not needed to explain what is known of spindle assembly and mechanics, and that many processes that are cited in support of the matrix hypothesis can be explained based on the properties of known components, in particular MTs and MT cross-linking and sliding motors (Sharp et al., 2000a). The MT cross-linking and sliding activities of motors could organize spindle MTs into an interconnected continuum consisting of rigid struts (the MTs) connected by multiple dynamic cross-linkers (the motors), producing a lattice capable of interconnecting chromosomes, spindle poles, and the cortex, with mechanical properties similar to many of those predicted of a spindle matrix (Fig. 2 B).

At least three mitotic motors have been proposed to function as MT–MT cross-linking and sliding motors, namely COOH-terminal kinesins like Ncd, with motor domains

connected by a rod domain to a nucleotide-insensitive MT binding site, bipolar kinesins like KLP61F with motor domains on both ends of a central rod domain, and dynein, which has been proposed to form cross-linking oligomers via an interaction with dynactin and NuMA (Merdes and Cleveland, 1997; Sharp et al., 2000a; Wittman et al., 2001; Fig. 2 B). The cross-linking of spindle MTs by these motors could organize MTs into interpolar and kinetochore bundles, form the interconnections between ipMT and ktMT bundles that occur throughout the half-spindles, exert outward and inward forces on spindle poles, and organize spindle poles in anastral spindles.

For example, in a "typical" amphiastral (centrosome-containing) spindle like that of the PEK cell, only a fraction of the minus ends of the MTs are attached to centrosomes at the poles, the remainder being distributed throughout the half-spindles, and there are extensive interactions between MTs of the kinetochore and interpolar fibers throughout the half-spindles (Mastronarde et al., 1993). The integrity of this structure would appear to require extensive connections throughout, and MT–MT cross-linking motors could fulfill this role. Several workers have postulated that motors organize the poles of amphiastral spindles. For example, the injection of dynein inhibitors causes the disorganization of some amphiastral spindles (Echeverri et al., 1996; Gaglio et al., 1997), but whether this reflects a specific loss of MT organization at the pole, or the disruption of MT–MT cross-links throughout the spindle as a whole is not obvious. The motor-dependent cross-linking of centrosome-bound MTs to the free minus ends of spindle MTs could also attach centrosomes to the poles of amphiastral spindles, explaining why the inhibition of dynein sometimes causes centrosomes to detach from spindles (Heald et al., 1997; Robinson et al., 1999). However, we note that centrosomes sometimes detach from spindles in the absence of dynein (or other motor) inhibitors (Murray et al., 1996; Debec et al., 1996; unpublished data).

A specific role for MT–MT cross-linking motors in the organization of spindle poles is more obvious in anastral spindles, like those of the *Drosophila* female meiosis I spindle and frog extract M-phase spindles assembled around chromatin beads, where the cross-linking and sliding activities of motors clearly zip together MTs and focus the poles (Merdes and Cleveland, 1997). This is apparent when one compares the functions of the MT–MT cross-linking and sliding COOH-terminal kinesin Ncd in amphiastral *Drosophila* embryonic spindles with anastral meiotic spindles. In the former case, Ncd exerts inward forces on spindle poles so that loss of Ncd function allows spindles to assemble too quickly, giving rise to morphologically disorganized yet functional spindles (Sharp et al., 2000b). In anastral oocyte spindles on the other hand, Ncd appears to be capable of directly cross-linking parallel MTs and moving towards the minus ends of MTs, thereby focusing them at the poles (Matthies et al., 1996), and by transporting Msps to the poles, Ncd could contribute to the stabilization of these focussed poles (Cullen and Ohkura, 2001).

Conclusions

No one can seriously doubt that MTs and MT-based motors are major components of the spindle fibers that help coordinate

chromosome movements, but whether the spindle contains another mechanical element, the matrix, made of proteins such as skeletor, remains a fascinating but unproven issue. It is interesting to note that the physical reality of the spindle fibers themselves was once a topic of vigorous debate (Schrader, 1944). Whether the discovery of skeletor will one day be seen as an important step in establishing the reality of the elusive spindle matrix is something that only the future knows.

Our work on mitosis is supported by a National Institutes of Health grant (GM55507) to J.M. Scholey.

Received: 29 January 2001

Accepted: 20 June 2001

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